REMARKS

Claims 74 and 79 have been amended. Claims 78, 80, and 81 have been cancelled. Claims 74, 79, and 82-93 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 74, 80, 82-84, and 86-93 under 35 U.S.C. § 103

Claims 74, 80, 82-84, and 86-93 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136, 1989) in view of Lereclus *et al.* (WO 94/25612) for the reasons of record. The Office Action stated:

> As applicant himself/herself can observe the high level of beta galactose (beta gal) production in strain harboring pH7902'LacZ , which was higher than the two strains harboring the other two plasmids in Figure 5, somehow undermine the levels of galactose production in strain harboring pHT7901'. However, if applicant reviews column 17 of U.S. patent 6,140,104 (lines 25-30), it is indicated that strain harboring pHT7901'LacZ produced a small but significant increase in beta gal production (i.e. 1200 Miller units from t-2 to t7.5 relative to 800 miller units beta gal activity produced in a strain harboring pH304'lacZ in the same period of time). Therefore, in contrast to applicants view, one of ordinary skill in the art did observe what he/she was expected (i.e. a significant increase in beta galactose production) when he/she combined the effect of "downstream region" with that of the heterologous promoter of lacZ gene.

This rejection is respectfully traversed for the reasons of record and further for the reasons discussed below.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966).

Hung *et al.* teach a *Bacillus subtilis* cell comprising a DNA construct comprising a consensus *bla* promoter originated from *E. coli*, having the sequence TTGACA for the -35 region and TATAAT for the -10 region, operably linked to a mouse dihydrofolate reductase (DHFG) encoding gene.

Lereclus *et al.* teach an expression system comprising a *cryIIIA* gene, under the control of a

cryIIIA promoter as well as a *cryIIIA* sequence called the "downstream region" or a "mRNA processing/stabilizing sequence", situated between the promoter and the coding sequence to be expressed and susceptible of acting at the post-transcriptional level during gene expression.

The Office asserts that "Applicant can appreciate that 1200 miller units of activity (corresponding to strain harboring pH7901'lacZ) shows a 50% increase (1200-800/800=50%) in beta gal production relative to strain harboring pH304'lacZ and such increase is sufficient and significant enough to motivate one of ordinary skill to insert the 'downstream region' of Lereclus into the *Bacillus* host comprising the DNA construct of Hung with a reasonable expectation of obtaining higher gene expression". Applicants respectfully disagree that the alleged increase is sufficient and significant enough to motivate one of ordinary skill for several reasons.

First, Lereclus *et al.* suggest on column 17, lines 29-30, that the level of production indicates "a small but significant increase of the beta-galactosidase activity during sporulation", but provide no statistical analysis that the "small but significant increase" is statistically significant. Lereclus *et al.* provide no error bars or P test results. Lereclus *et al.* state on column 14, lines 51-53: "The specific activities presented (expressed in Miller units per milligram of protein) correspond to the mean values of at least two independent experiments." One of ordinary skill in the art would have performed the experiment numerous times because of the alleged low level of beta-galactosidase activity and then performed a statistical analysis on the data to determine its statistical significance.

Second, Lereclus *et al.* did not perform a proper negative control involving no promoter driving the *lacZ* gene and, therefore, the low beta-galactosidase activity allegedly observed for pHT304'lac and pHT7901'lac may be merely background levels. Consequently, the calculation made by the Office cannot be relied upon as statistically significant because of this missing information.

Third, the time course for pHT304'LacZ (Figure 5) shows slightly higher beta-galactosidase activity for approximately the first half of the time course while pHT7901'LacZ is slightly higher during the second half. One of ordinary skill in the art would expect the mRNA stabilizing sequence to stabilize the message throughout the entire time course. Consequently, one skilled in the art would not expect the beta-galactosidase activity for pHT901'LacZ to be lower relative to pHT304'LacZ in the earlier time points as seen in Figure 5 if the mRNA stabilizing sequence was truly exerting a stabilizing effect. Rather, one of ordinary skill in the art would expect the beta-galactosidase activity for pHT7901'LacZ to be higher throughout the time course relative to pHT304'LacZ.

Fourth, the results obtained with pHT7902'LacH versus the results obtained with pHT304'lacZ and pHT7901'lacZ show that the alleged increase in beta-galactosidase production obtained with pHT7901'lacZ was only approximately 1% of the increase in beta-galactosidase production obtained with pHT7902'lacZ. The Office points out that a *prima facie* case of obviousness does not require overwhelming data in support of combining references but a mere motivation. However, the Office appears to rely solely on the curves for pHT304'lacZ and pHT7901'lacZ in Figure 5 to support its argument without consideration of the pHT7902'lacZ results. In Applicants' view, one of ordinary skill in the art would have taken all of the data in Figure 5 into consideration and concluded that operably linking the *lacZ* promoter with the *cryIIIA* mRNA stabilizing sequence may have a "small" effect if at all since no statistical evidence is provided while the *cryIIIA* promoter operably linked to its mRNA stabilizing sequence produces the highest level of beta-galactosidase expression among the constructs shown in Figure 5.

Fifth, the results in Table 1 of Applicants' specification show that when the *cryIIIA* promoter and *cryIIIA* mRNA stabilizing sequence are operably linked to the Savinase coding sequence, the relative activity increases to 350% from 100% with only the *cryIIIA* promoter and when the "short" consensus *amyQ* promoter and *cryIIIA* mRNA stabilizing sequence are operably linked to the Savinase coding sequence, the relative activity increases further to 620%. Lereclus *at al.* do not teach this trend. In fact, one of ordinary skill in the art would have concluded that Lereclus *at al.* never performed the proper test of placing the *cryIIIA* mRNA stabilizing sequence downstream of a heterologous promoter known to function well in a *Bacillus* host cell. The *lacZ* promoter is well known in the art to be simply too weak in a *Bacillus* host cell to make any valid conclusion.

Based on the reasons above, Applicants submit that one of ordinary skill in the art would have been motivated to use the *cryIIIA* promoter with its native mRNA stabilizing sequence and not the *lacZ* promoter with the *cryIIIA* mRNA stabilizing sequence because the results teach that there is no reasonable expectation of success of using the *cryIIIA* "downstream region" with promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene.

However, to further prosecution of the instant application, Applicants have amended claim 74 to recite: "A *Bacillus* cell comprising a nucleic acid construct which comprises (a) a "consensus" promoter of a *Bacillus amyloliquefaciens* alpha-amylase gene (*amyQ*) having the sequence TTGACA for the "-35" region and TATAAT for the "-10" region operably linked to a single copy of a nucleic acid sequence encoding a polypeptide, and (b) a *cryIIIA* mRNA processing/stabilizing sequence located downstream of the "consensus" promoter and upstream of the nucleic acid sequence encoding the polypeptide, wherein the mRNA processing/stabilizing sequence increases

expression of the nucleic acid sequence encoding the polypeptide". However, Applicants reserve the right to file a continuing application(s) to the cancelled subject matter.

Most inventions arise from a combination of old elements, and each element may often be found in the prior art. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (citing *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983)). The mere identification of each element in the prior art, however, is insufficient to defeat the patentability of the combined subject matter as a whole. *Id.* Rather, one must show a motivation to combine the references, *i.e.*, "reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.*

A patent claim is obvious over a combination of prior art references only when "the prior art would have suggested to one of ordinary skill in the art that [the claimed invention] should be carried out and would have a reasonable likelihood of success... . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical,* 837 F.2d 469, 473 (Fed. Cir. 1988); *see also,* 35 U.S.C. § 103. An invitation to experiment, alone, cannot make an invention obvious. *In re Dow*, 837 F.2d at 473.

Based on the discussion above, there is no suggestion or motivation in Hung *et al.* in view of Lereclus *et al.* to construct and use a *Bacillus* cell comprising a nucleic acid construct which comprises (a) a "consensus" promoter of a *Bacillus amyloliquefaciens* alpha-amylase gene (amyQ) operably linked to a single copy of a nucleic acid sequence encoding a polypeptide, and (b) a *cryIIIA* mRNA processing/stabilizing sequence located downstream of the "consensus" promoter and upstream of the nucleic acid sequence encoding the polypeptide, that increases expression of the polypeptide. Hung *et al.* in view of Lereclus *et al.* is merely an invitation to experiment. An invitation to experiment, alone, cannot make an invention obvious. *Id.*

At most, Hung *et al.* in view of Lereclus *et al.* only makes it obvious to try to construct and use such a *Bacillus* cell. However, the "obvious to try" standard is inadequate to render the claimed invention obvious without some teaching in the prior art which gives a reasonable expectation of success in achieving that goal. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

For the foregoing reasons, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

II. The Rejection of Claim 78 under 35 U.S.C. § 103

Claim 78 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus (WO 94/25612) further in view of Diderichsen (*Res. Microbiol.* 142: 7-8, 793-96, 1991) for the reasons of record. This rejection is respectfully traversed for the reasons of record and further for the reasons below

Hung *et al.* and Lereclus *et al.* are discussed in Section I above.

Diderichsen discloses using *amyQ* and *amyM* promoters in enhancing expression of a *Bacillus stearothermophilus* alpha-amylase (*amyS*) gene in *Bacillus subtilis* and displays a 3-fold increase in *amyS* productivity compared to an equivalent *B. subtilis* construction.

For the reasons stated in Section II, Applicant submits that the rejection under 35 U.S.C. § 103(a) has been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

III. The Rejection of Claim 85 under 35 U.S.C. § 103(a)

Claim 85 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus (WO 94/25612) further in view of Jorgensen (WO 96/23073) for the reasons of record. This rejection is respectfully traversed for the reasons of record and further for the reasons below.

Hung *et al.* and Lereclus *et al.* are discussed in Section I and Jorgensen in Section II above.

For the reasons stated in Section II, Applicant submits that the rejection under 35 U.S.C. § 103(a) has been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

IV. The Rejection of Claims 89-90 under 35 U.S.C. § 103

Claims 89-90 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus *et al.* (WO 94/25612) further in view of Jorgensen *et al.* (WO 93/10249) for the reasons of record. This rejection is respectfully traversed for the reasons of record and further for the reasons below.

Hung *et al.* and Lereclus *et al.* are discussed in Section I above.

Jorgensen *et al.* disclose a *Bacillus* promoter derived from a variant of a *Bacillus licheniformis* alpha-amylase promoter for use in expressing heterologous genes.

For the reasons stated in Section I, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the

rejection.

V. The Provisional Rejection of Claims 74 and 78-93 under the Doctrine of Obviousness-Type Double Patenting

Claims 74 and 78-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-31 of U.S. Patent No. 5,955,310. The Office Action stated:

> Claims 74, 78-93 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-31 of U.S. Patent No. 5,955,310. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of issued claims embrace the scope of instant claims.

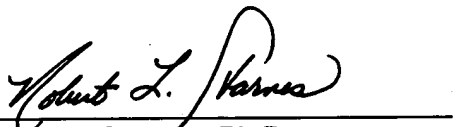
Applicants submit a terminal disclaimer in compliance with 37 CFR 1.321(c).

For the foregoing reason, Applicants submit that the claims overcome this rejection and respectfully request reconsideration and withdrawal of the rejection.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



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